

Amendments To The Specification:

Please replace the paragraph on page 21, lines 13-25, with the following amended paragraph:

The 5' untranslated region contains a promoter or RNA polymerase binding sequence, such as those for the T7, T3, or SP6 RNA polymerase. Positioned downstream of or within the promoter region is a DNA sequence, which codes for a ribosomal binding site. This ribosome binding site may be specific for prokaryotic ribosomal complexes (including ribosomal RNAs) if a prokaryotic translation procedure is used. However, a preferred embodiment of this invention uses a eukaryotic sequence and an in vitro eukaryotic translation system, such as the rabbit reticulocyte system (Krawetz *et al.*, 1983 *Can. J. Biochem. Cell. Biol.* 61:274-286; Merrick, 1983 *Meth. Enzymol.* 101:38). A consensus translation initiation sequence, GCCGCCACCATGG (SEQ ID NO: 33), as well as other functionally related sequences have been established for vertebrate mRNAs (Kozak, 1987 *Nucleic Acids Res*, 15:8125-8148). This sequence or related sequences may be used in the DNA construction to direct protein synthesis in vitro. The ATG triplet in this initiation sequence is the translation initiation codon for methionine; in vitro protein synthesis is expected to begin at this point.

Please replace the paragraph on page 22, lines 4-14, with the following amended paragraph:

In addition, SEQ ID NO: 1 encoding DNA may be incorporated into the in vitro expression unit. Within one embodiment, the expressed polypeptides contain both carrier polypeptide/peptide and SEG ID NO 1. The carrier peptide would be useful for quantifying the amount of fusion polypeptide and for purification (given that an antibody against the carrier polypeptide is available or can be produced). One example is 6His amino acid sequence (SEQ ID NO: 40); the second is the 11 amino acid Substance P, which can be attached as fusion peptides to peptides of the invention. Anti-6 His (6xHis: SEQ ID NO: 40) and anti-Substance P antibodies are commercially available for detecting and quantifying fusion proteins. Another example is the eight amino acid marker peptide, "Flag" (Hopp *et al.*, 1988 *Bio/Technology* 6:1204-1210),. A preferable

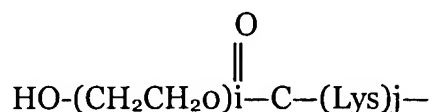
form of the carrier polypeptide is one, which may be cleaved from the novel polypeptide by simple chemical or enzymatic means.

Please replace the paragraph on page 24, lines 1-11, with the following amended paragraph:

Various methods for constraining the secondary structure of a peptide are well known in the art. For example, peptides such as those containing -Phe-Pro-Gly-Phe- sequence (SEQ ID NO: 37) form -turn, a well-known secondary structure. For example, a peptide can be stabilized by incorporating it into a sequence that forms a helix such as an alpha helix or a triple helix, according to methods described, for example, by Dedhar *et al.*, (1987) *J. Cell. Biol.* 104:585; by Rhodes *et al.*, (1978) *Biochem* 17:3442; and by Carbone *et al.*, (1987) *J. Immunol* 138:1838, each of which is incorporated herein by reference. Additionally, the peptides can be incorporated into larger linear, cyclic or branched peptides, so long as their receptor-binding activity is retained. The peptides of the present invention may be of any size so long as the VEGF receptor-binding activity is retained, however, in one embodiment, peptides having twenty or fewer total amino acids are preferred.

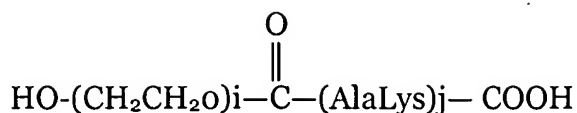
Please replace the paragraph on page 43, line 18, to page 44, line 3, with the following amended paragraph:

Examples of useful segmented copolymers containing polypeptides include the poly(oxyethylene)-poly-L-lysine) diblock copolymer of the following formula:



(XVIII)

wherein *i* is an integer of from about 2 to about 500, and *j* is an integer from about 4 to about 500 ((Lys)_j is disclosed as SEQ ID NO: 42). A second example is the poly(oxyethylene)-poly-(L-alanine-L-lysine) diblock copolymer of formula:



(XIX)

wherein i is an integer of from 2 to about 500, and j is an integer from about 2 to about 500 ((AlaLys) j is disclosed as SEQ ID NO: 43).

Please replace the paragraph on page 60, lines 23-32, with the following amended paragraph:

Synthesis CONJUGATE NO.: 3 (polylysine-PEG1500-peptide (SEQ ID NO: 3))

The conjugates ID NO 3 was prepared using di-amino derivative of polyoxyethylene MW 1500 (PEG-bis-amine MW 1500 from Shearwater Polymers, Inc. Al., Cat. No. PT-017-08). PEG-bis-amine was reacted, with SPDP (N-Succinimidyl 3-[2-pyridyldithio]propionate, from Sigma, Cat. No. P-3415), and the resulting PEG-bis-SS-pyridyl was purified with HPLC, (step 1). Polylysine (H-Lys)₈(H-Lys)₄(Lys)₂LysCysNH₂ (SEQ ID NO: 38) was synthesized according to the protocols described in Example 1 (step 2). Peptide SEQ ID NO: 3 was reacted with excess of PEG-bis-SS-pyridyl, followed by adding of an excess of polylysine to the reaction (step 3). The progress of the conjugation reaction was monitored by light UV absorption at 340 nm. Upon completion, the components of the reaction mixture were separated using HPLC.

Please replace the paragraph on page 61, lines 12-23, with the following amended paragraph:

2. Solid Phase Synthesis of Polylysine (H-Lys)₈(H-Lys)₄(Lys)₂LysCysNH₂
(SEQ ID NO: 38)

The synthesis of polylysine was performed using 0.5 g (0.1 mmol) of NovaSyn TGR resin (Nova Biochem, Cat. No. 01-64-0060), using Fmoc-Cys(TRT)-OH for the first cycle of the synthesis, and Fmoc-Lys(Fmoc)-OH for next four synthetic cycles. Each synthetic cycle consisted of steps 1-3 of the Example 1. The reaction was completed with Fmoc-deprotection (step 1 of the Example 1), and cleavage (step 6 of the Example 1). The

product was purified on HPLC using Vydac C18 preparative column (25x2.25 cm). The column was eluted with a two-component eluent gradient 0.5% per minute, starting from 0% of solution B in solution A, at flow rate 5 mL/min. Solution A was 0.1% TFA in H₂O, and solution B was 0.1% TFA in CH₃CN. Fractions were identified by electrospray MS, and by dark blue color developed after mixing sample with 1% ninhydrin in buthanol (1:1 v/v) at 120°C. for 1 min. The yield of freeze-dried product (polylysine) was 21 mg.

Please replace the paragraph on page 73, line 19, to page 74, line 22, with the following amended paragraph:

List of Oligonucleotide Sequences

- (1) SEQ ID NO: 9 (ONV5.2)
(A) LENGTH: 69 nucleotides
(B) TYPE: nucleotide

**GG GCC GGT AAC GGG TAC GAG ATC GAG TGG TAC TCG TGG GTC ACG CAC
GGG ATG TAC GGT GGC GCT TCT G**

Gln Gly Tyr Glu Ile Glu Trp Tyr Ser Trp Val ~~The~~Thr His Gly Met Tyr (SEQ ID NO: 34)

- (2) SEQ ID NO: 10 (ONV5.10)
(A) LENGTH: 69 nucleotides
(B) TYPE: nucleotide

**GG GCC GGT CCG GAG CCC GAG GTC CGG TTG AGT CCG CCG GGT CAT ATC
CAG TCG CTC GGT GGC GCT TCT G**

Pro Glu Pro Glu Val Arg Leu Ser Pro Pro Gly His Ile Gln Ser Leu (SEQ ID NO: 35)

- (3) SEQ ID NO: 11. (ONV40)
(A) LENGTH: 69 nucleotides
(B) TYPE: nucleotide

**GG GCC GGT TTT GTG GGG GGG TGG TTG GTT CCG GAG GAC GAG CGG CTC
TAC CCG GAG GGT GGC GCT TCT G**

Phe Val Gly Gly Trp Leu Val Pro Glu Asp Glu Arg Leu Tyr Pro Glu (SEQ ID NO: 36)

(4) SEQ ID NO: 12 (ON 10)

(A) LENGTH: 10 nucleotides

(B) TYPE: nucleotide

AAGCGCCACC

(5) SEQ ID NO: 13 (ON 11)

(A) LENGTH: 11 nucleotides

(B) TYPE: nucleotide

ACCGGCCCCGT

Please replace the paragraph on page 79, lines 4-18, with the following amended paragraph:

Ability of peptides to inhibit the endothelial cell proliferation

Endothelial cells, for example, human umbilical vein endothelial cells (HUVEC) which can be prepared or obtained commercially (Clonetics, San Diego, Calif.) are plated onto 96-well plates (Costar) at 10^4 cells per well in 200 μ l of EGM-2 medium (Clonetics) supplemented with 0.5% heat-inactivated fetal bovine serum. Cells are allowed to grow for 24 hours at 37°C. under 5% CO₂. Recombinant human VEGF is added to the wells (at 10 ng/ml final concentration) along or with the test compound (SEQ ID NO: 4) at various concentrations: 0 uM; 0.5 uM; 1 uM; 5 uM; 25 uM; 50 uM. Non-relevant peptide YAFGYPS (SEQ ID NO: 39) at the same concentration is used as control. After 48 hours of incubation at 37°C. under 5% CO₂, 1 μ gCi of [methyl-³H]-thymidine (20 Ci/mmol; ICN) is added per well and plates are incubated for an additional 24 hours. The cells are then placed on ice, washed twice with EGM-2 medium containing 10% FBS and fixed for 10 minutes by adding 200 μ l of ice-cold 10% trichloroacetic acid per well. After washing with ice-cold water, cells are lysed and DNA is solubilized in 50 μ l of 2% SDS. [³H]-Thymidine incorporation is determined by scintillation counting. Results are presented

in Table 8 and expressed as the average of 3 different wells for each concentration of compound.

Please replace Table 14 on page 81, with the following amended table:

Table 14.

Clone	Insert sequence	SEQ ID NO:	Binding to hFlt-1 in %
V5.2	NGYEIEWYSWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	1	100
N1/A	AGYEIEWYSWVTHGMY (Ala-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	14	42.93± 25.76
E4/A	NGYAIEWYSWVTHGMY (Asn-Gly-Tyr-Ala-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	15	17.54± 5.31
I5/A	NGYEAIEWYSWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Ala-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr) (Asn-Gly-Tyr-Glu-Ala-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	16	18.76± 0.26
E6/A	NGYELAWYSWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Ala-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	17	19.155± 14.07
W7/A	NGYEIEAWSWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Ala-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	18	66.23± 27.07
Y8/A	NGYEIEWASWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Ala-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	19	67.035± 6.28
S9/A	NGYEIEWYAWVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ala-Trp-Val-Thr-His-Gly-Met-Tyr)	20	101.69± 16.70
W10/A	NGYEIEWYSAVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ala-Trp-Val-Thr-His-Gly-Met-Tyr) (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Ala-Val-Thr-His-Gly-Met-Tyr)	21	22.08± 7.19
T12/A	NGYEIEWYSWVAHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Ala-His-Gly-Met-Tyr)	22	62.63± 22.58
H13/A	NGYEIEWYSWVTAGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-Ala-Gly-Met-Tyr)	23	55.34± 10.78
M15/A	NGYEIEWYSWVTHGAY (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Ala-Tyr)	24	78.24± 19.42
Y16/A	NGYEIEWYSWVTHGMA (Asn-Gly-Tyr-Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Ala)	25	15.30± 15.27
E46/A	NGYALAWYSWVTHGMY (Asn-Gly-Tyr-Ala-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	26	44.46± 7.05
W710/A	NGYEIEAWSAVTHGMY (Asn-Gly-Tyr-Glu-Ile-Glu-Ala-Tyr-Ser-Ala-Val-Thr-His-Gly-Met-Tyr)	27	62.15± 22.16
V5.2/1	EIEWYSW (Glu-Ile-Glu-Trp-Tyr-Ser-Trp)	28	6.55± 15.81
V5.2/5	EIEWYSWVTHGMY (Glu-Ile-Glu-Trp-Tyr-Ser-Trp-Val-Thr-His-Gly-Met-Tyr)	29	85.6± 22.61

Please replace the paragraph on page 82, lines 16-19, with the following amended paragraph:

Synthetic oligonucleotide encoded peptide SEQ ID NO: 1 flanked with restriction sites and SerGlyAlaGly linker (SEQ ID NO: 41) was synthesized (5'ACAACCTCTAGAATGAACGGGTACGAGATCGAGTGGTACTCGTGGGTCACGCACGGGATGTACTCTGGGGCCGGATCTAGACAACA SEQ ID NO: 32).